

National Institutes of Health FY 2004 Congressional Justification

Fiscal year 2004 marks a decisive turning point for the National Institutes of Health (NIH). Over the past five years, the NIH budget doubled and those funds led to advances that helped revolutionize basic and clinical research. Alongside the stunning achievement of sequencing the human genome, stand dramatic advances in research technologies, such as DNA arrays, which permit investigators to study the activity of thousands of genes at once. The swift and deep impact of such advances is already radically altering the way physicians diagnose, treat, and prevent diseases, such as arthritis, hypertension, heart disease, diabetes, and Alzheimer's disease. There is more to come.

Today, NIH is poised to further its successes in reducing death and suffering from cardiovascular disease, stroke, AIDS, and hepatitis B and C, among others. We must confront emerging challenges, such as conquering the epidemic of obesity, better managing chronic diseases, exploring the promise of stem cells, and focusing on aging of the population and the persisting disparities in health among different segments of our population.

The FY 2004 budget will enable the NIH to continue its historical mission – to uncover new knowledge that can lead to better health for everyone. We will explore living systems even more deeply by encouraging investigators to study mysteries of the communication and regulation of activities within and between cells. Even greater attention will be drawn to the science central to confronting new and immediate threats, such as bioterrorism. This biodefense challenge, which affects our country's national security, must engage our nation's best scientists.

The NIH determines how best to capitalize on available scientific opportunities and improve clinical investigation so that new knowledge can be translated into innovative prevention strategies, diagnostics and treatments. The agency oversees multiple fields of research to identify gaps in knowledge as well as needs in training and infrastructure. It plays an essential role by serving as a public forum for exchanging scientific and health information.

In fulfilling its mission, the NIH leadership manages a diverse portfolio of research founded on both public health need and scientific opportunity. It does so with the advice of, and in collaboration with, our partners: scientists, patients, physicians, health care payers and providers, the public, the Congress, and the Administration. The two-tiered NIH peer review system is critical to ensuring that only the best proposals are funded from approximately 44,000 research and training applications received each year.

On the largest campus for biomedical research in the world, the Directors of its 27 Institutes and Centers support an extramural research community of more than 50,000 scientists affiliated with approximately 1,700 organizations, including universities, medical schools, hospitals, and other research facilities located in all 50 states, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and points abroad.

The NIH also sustains an in-house, or intramural, program of basic and clinical research managed and staffed by world-class physicians and scientists. This intramural research program, which includes the NIH Clinical Center, gives our nation the unparalleled ability to respond immediately to health challenges nationally and worldwide.

The NIH helps to ensure a continuing strong scientific enterprise by supporting research training and career development programs, the acquisition of the most modern scientific equipment and instruments, and the establishment and maintenance of research clinics and laboratories for its investigators.

NIH-funded programs complement the research and development (R&D) funded by for-profit entities by focusing on research for which risks are too high or financial incentives too low to attract private investment. These areas include basic research as well as evaluation of non-commercially viable, yet critical, interventions such as diet, exercise, and new uses of off-patent pharmaceuticals. It also includes public health concerns such as biodefense, the special needs of vulnerable populations, as well as rare diseases that lack private sector interest.

The NIH continually monitors and evaluates the scientific landscape for new opportunities and challenges through its established advisory bodies and its specialized review sections, including regular outside review of its own programs. NIH seeks public input through groups such as the NIH Council of Public Representatives (COPR). The Agency also translates data from scientific discoveries into information for use by the public and health care providers. The general public accesses the NIH Web site more than almost any other Federal Web source.

Changing Landscape

The scientific discoveries funded through the dramatic funding increases over the last five years transformed the biomedical landscape – a transformation so profound that it requires the NIH to sharpen the focus of its strategies for rapidly developing and disseminating new knowledge to improve the nation's health.

To address cross-cutting research needs and to ensure the judicious investment of funds, the Agency is carefully charting the biomedical terrain by constructing a Roadmap for priority actions and initiatives.

To put the Roadmap in perspective, we highlight the value of biomedical research sponsored by the NIH in dramatically reducing the mortality and suffering caused by specific diseases. For example, NIH discoveries helped achieve:

- * 61 percent reduction in age-adjusted cardiovascular mortality rates since 1968;
- * 61 percent reduction in age-adjusted stroke mortality rates since 1972;
- * 70 percent reduction in AIDS deaths since 1995;
- * near eradication of *Hemophilus Influenzae* in children, a major cause of acquired mental retardation;
- * striking reduction in transmission of blood transfusion-related diseases, such as hepatitis B and C, and HIV making the U.S. blood supply the safest in the world; and
- * decline in the age-adjusted rates of death for all cancers (from about 215 to 203 deaths per 100,000 in 1998) since 1992.

While we celebrate this increase in life expectancy and quality of life in a number of arenas of health, the research achievements that made them possible also shifted the burden of disease. As a case in point, decreased mortality from acute disease parallels a significant rise in the burden of chronic diseases and the emergence of new challenges in aging and degenerative diseases.

Here are three examples of how the burden of disease shifted.

First, improved prevention and treatment reduced early deaths from coronary heart disease. As life expectancy increased for this group of patients, more persons survived with chronic congestive heart failure, a condition more common in the older population.

Second, with earlier detection of cancer and improved treatment, the five-year survival rates increased from over 49 percent for persons diagnosed with cancer in 1975 to nearly 62 percent for persons diagnosed in 1993. Now, more than 8.4 million Americans live with a history of cancer. And these cancer survivors require chronic and long-term interventions to prevent recurrences.

Third, from 1985 to 2001, the mean survival time for the one child in 2,500 born with cystic fibrosis (CF) increased from 25 to 33.4 years. This increase in survival resulted directly from new and better treatments achieved through NIH- funded research. Ninety-three percent of CF patients take pancreatic enzymes to aid digestion and nutrition. Over the past year, 44 percent received at least one course of an inhaled antibiotic that helps them avoid hospitalization. With improved nutritional therapy over the past decade, mean weight increased by 5 to 10 percent for CF patients under 20 years of age; and CF patients today are closer to normal height.

Because of our success in battling these more acute and lethal diseases, we now witness an increase in chronic health conditions. Further, the aging U.S. population accounts, in part, for the increase in costs associated with chronic diseases – these make up 75 percent of today's health care costs. To salvage and secure the health of our nation, researchers must confront the challenge posed by these chronic conditions, including the alarming epidemic of obesity and its consequences.

While we address these new challenges, we must also continue attacking today's major killers – coronary heart disease, stroke, cancer, and diabetes – and eliminate the impact of both acute and chronic illness on vulnerable subgroups of our diverse population, such as the poor and racial and ethnic minorities.

Today, the call for breakthrough research becomes ever more urgent, especially against the backdrop of the increasing burden of economic and human costs in the changing landscape of natural and man-made health threats. Rapid advances in our understanding and mastery of the life sciences must, therefore, rank high on the list of national priorities.

Failure to respond with determination and dedication will assuredly leave us vulnerable to an increasingly globalized environment where disease can spread easily. Rapid advances in fully understanding the complex biology of disease and the interplay of genetics, environment, and life style – all now within our reach – are without question the key to reducing the burden of disease and its cost to society.

Challenges and Opportunities

Completing the sequencing of the human genome marks the close of only the first phase in our quest for a complete understanding of the human organism in health and disease. The new era in the biomedical sciences will

be marked by immense scientific complexity and enormous promise for preventing and curing disease.

What is the grand vision for this research? That one day we will not just cure disease when it occurs, but we will prevent the onset of certain diseases. This vision requires a dramatic rethinking of both the strategies and research methods most likely to lead to rapid progress in FY 2004 and beyond.

The NIH Roadmap

Given its extensive and complex program portfolio and the need to invest funds productively for the health and defense of the American people, NIH launched an Agency-wide effort to identify the critical roadblocks and knowledge gaps that

constrain rapid advances in biomedical research progress.

The NIH Roadmap is the result of an ongoing series of consultations with scientists charged with thinking broadly about the future. It is comprised of three broad initiatives which will exploit and extend past discoveries to meet tomorrow's challenges:

- I. New Pathways to Discovery
- II. Multidisciplinary Research Teams of the Future
- III. Re-engineering the Clinical Research Enterprise

I. New Pathways to Discovery: New Approaches and Technologies

New Approaches: A comprehensive parts list for biology

Investigators who sequenced the human genome took a significant step in unlocking the complexities of human disease. This significant achievement is opening new research pathways, leading to a better understanding of fundamental biological processes and leading to the development of complementary and cutting-edge technologies.

To understand the role of genetics in disease, we must comprehend how genes manage the production of proteins, the building blocks of the body's cells and tissues. That means identifying all of the components of the human cell – all of the genes and their common variants, all of the regulatory signals that control gene expression, and all of the proteins those genes encode. Even more importantly, we must understand how those components go awry in disease.

Genetic variations hold the key to understanding disease mechanisms. An important goal for NIH is to catalog genetic variations and discern if and how they are associated with disease risk. NIH and its international partners are creating a catalogue of single nucleotide polymorphisms (SNPs) and determining how those variants are correlated in “DNA neighborhoods.” Such neighborhoods are called “haplotypes.” NIH is leading a major new initiative, the international haplotype map consortium, involving laboratories in five countries and active participation by the private sector. This project will develop a haplotype map for the entire genome. By making such a powerful new database available, scientists will be able to find genes for common diseases like diabetes, heart disease, cancer, and mental illness faster, more efficiently, and more affordably. Ultimately, this approach will narrow the search for the disease-causing alterations in the genome and speed the development of novel diagnostics and drugs that are tailored to patients' genetic profiles.

A critical component of the parts list relates to the proteins. “Proteomics” studies the complete set of an organism's proteins or its “proteome.” It is an area of research in which investigators separate, identify, and characterize proteins to better understand their functions and the regulation of their functions. Proteomics offers an important tool for developing preventive therapeutics. Systematic proteomic approaches toward pharmaceutical research will not only improve treatment, but could also lower the cost of drug development by boosting the industry's success rate. Advances in miniaturized fabricated devices such as protein microarray technology have already allowed multiple and rapid screening of compounds in the drug development process.

New Approaches: Integrative Pathways and Networks in Health and Disease

Biological processes are not simple or static. Integrative research is focused on understanding how complex biological systems operate, with the goal of being able to predict the behavior of the system in response to disturbances such as disease or experimental medications. By understanding how the components of a network interact, investigators can identify the many and

varied parts of the system that play a role in the disease process. And because most diseases involve multiple points of failure in several key biological pathways, this research is becoming ever more critical.

For example, the cell operates using an enormously complex pattern of interactions. Signals are sent from various compartments (such as from the cell surface to the nucleus) using complex pathways made up of multiple proteins. Those pathways interconnect to constitute highly regulated networks that permit the cell to respond in a myriad of ways to its circumstances. Understanding such complex networks is a very high priority, as they will provide critical clues to disease pathogenesis and new ideas for drug therapy.

New Approaches: Regenerative Medicine

Regenerative medicine seeks to revolutionize the ways we improve the length and quality of life by restoring, maintaining, or enhancing tissue and organ function. It involves the merging of several fields, including tissue engineering, biomaterials development, and stem cell biology. Tissue engineering includes research on the growth of regenerating cells in two and three-dimensional matrices for use in transplantation therapies to replace a damaged or diseased organ. Novel biomaterials are being designed to provide both physical and chemical cues, which direct the organization, growth, and differentiation of cells in the process of forming functional tissue.

A major component of regenerative medicine is stem cell biology, including animal and human, adult and embryonic stem cells. NIH is actively working to develop the physical and intellectual infrastructure needed to capitalize on the opportunity afforded by research using human embryonic stem cells allowable under the President's August 2001 policy (<http://www.nih.gov/news/stemcell/index.htm>). Thus, the NIH is initiating programs to attract more talented scientists to this emerging field and to integrate stem cell research with tissue engineering and biomaterials in order to capitalize on the promise of regenerative medicine for incurable diseases such as Type I diabetes.

New Technologies: Structural Biology

Structural biology, the study of protein structures, yields penetrating insights into both biological function and disease and the design and development of new drugs. Large and complex protein assemblies (a group of proteins that interact together) perform many of the numerous tasks in the cell. To date, NIH-funded researchers resolved over 18,000 protein structures. This work has led to the design of countless new drugs. But much more remains to be done. There are several hundred thousand structures that are yet to be resolved. The resolution of more large protein assemblies is still a formidable challenge that must be met if we are to ensure the most efficient and effective drug development.

Protein modeling is another approach to the identification of suitable targets for medications. Such efforts also promise to help us understand the effects of the slight genetic differences that

make one susceptible or resistant to given diseases. But despite recent progress, researchers still cannot predict protein structure from their building blocks (the amino acid molecules that make up proteins). To this end, we must engage computational biology and mathematical tools to fully exploit the ever-increasing protein sequence data provided by various genome projects.

New Technologies: Computational Biology and Bioinformatics

In recent years, two fields have stood out for their rapid progress and societal impact: biomedicine and computer science. The marriage of those two disciplines allows even more dramatic progress. Without major improvements in computational capability, the first draft sequence of the human genome could not have been obtained and distributed freely to all in 2001, ahead of schedule. Today, advances in biomedicine will depend significantly on computation and bioinformatics or data mining. One example of this dependence is seen in the clinical research enterprise, where, in the future, it will be possible to mine data from many patients to discover how to better treat each individual and to ask and answer questions that are currently not answerable.

A major challenge for the NIH is to improve the existing computational infrastructure for all of biomedical research. The NIH plans to improve existing databases and facilitate data sharing among researchers across all sectors, inside and outside NIH. Efforts will also focus on improving partnerships with other Federal agencies, such as the Department of Energy and the National Science Foundation (NSF). Such collaborations can build on activities already underway, including the NIH/NSF Biomath initiative, the NIH/NSF program in computer science, to name just two.

New Technologies: Molecular Libraries

Despite the recent and rapid discovery of biological targets with research and therapeutic potential, the identification of small molecules that selectively interact with and alter these targets is still a tedious and unpredictable process. Creating molecular libraries (comprehensive databases and repositories of chemical compounds, drugs, reagents, and molecular research tools) and enhancing access to screening services would facilitate the development and use of small molecules as novel research tools and potentially for new therapeutics. This effort represents an important opportunity for NIH to apply its unique resources, mandate, influence, and scientific leverage to provide access to needed research tools that will help accelerate researchers' ability to probe the function of the complex biological circuits which play a role in normal function and disease.

For this strategy to succeed, pharmaceutical and biotechnology companies must participate. For this reason, issues related to intellectual property must be addressed. To this end, the NIH will explore incentives to encourage private sector participation.

New Technologies: Nanotechnology

Nanotechnology, the science of building materials from single atoms and molecules, could significantly improve, if not radically change, the prevention, detection, diagnosis, and treatment of diseases and disorders. Operating at the same small scale as biological processes, nanotechnology offers a unique vantage point from which to view and interact with basic life processes.

Materials produced through nanotechnology could help repair damaged tissues, monitor critical clinical indicators, and act as an interface for electrical stimulation and measurement. Placed in the body, such materials would, in theory, not irritate or damage the surrounding tissues, nor impair their function. Instead, they would actively communicate with the host tissue and dissolve into harmless components that could be absorbed or excreted when no longer needed.

For the NIH, the challenge of applying nanotechnology to biomedicine in FY 2004 and beyond amounts to integrating the unique properties and performance achieved at the nanoscale to people, for example, by developing new diagnostic tools. In addition, nanotechnology could be the source of research methods at the scale of single cells and subcellular structures that could accelerate greatly our understanding of biology.

New Technologies: Molecular Imaging

In FY 2004, NIH plans to continue its investment in molecular imaging, a critical component of diagnostic tool development. Improved imaging technologies allow researchers to view complex structures such as protein assemblies, which carry out most cellular functions. Live and real time 3-D information not only provides researchers a key to understanding cell organization, but also crucial clinical data for understanding molecular processes which underlie complex disease. This, in turn, leads to better opportunities for disease intervention or prevention. This understanding will provide novel approaches to non-invasive diagnostics and monitoring, and minimally invasive therapy, for a wider range of organ systems and diseases.

II. Multidisciplinary Research Teams of the Future

There has been a fundamental shift in the way that science is being done in this country. While advances in genomics, proteomics, structural biology, systems biology, and bioinformatics have created unique opportunities for researchers to tackle complex biological and biomedical problems, a look inside the laboratories across the country reveals tremendous changes – changes in the workforce, the administration, the means and modes of collaboration, and in the training of investigators. The culture of individual investigators working in isolation – stoked by competition and fueled by ingenuity – is now being redirected to large teams that span university departments, disciplines, and geographical barriers. As we look to the future, the NIH will need

to address the role of government in facilitating culture change and work with the private sector, universities, professional societies, and researchers to implement such change.

To foster the creation of multi-disciplinary teams of experts in biology, behavior, engineering, mathematics, chemistry, physics, informatics, and clinical research, the NIH will initiate new programs that emphasize support for groups of investigators with diverse expertise who are able to bring forth proposals with novel prospects for scientific advances. NIH will also explore incentives to universities for infrastructure and training, and develop innovative strategies for the training of biological, behavioral, mathematical, and physical scientists across traditional departmental and disciplinary boundaries at both under- and post-graduate levels. In some cases, new scientific communities must be formed – biomedical research teams must integrate greater numbers of mathematicians, physicists, social scientists, and engineers. Ultimately, new scientific disciplines will be required and varied programs for interdisciplinary research training must be developed at multiple institutions across the country.

III. Re-engineering the Clinical Research Enterprise

The need for a strong clinical research enterprise is bidirectional: from bench to bedside to translate basic discoveries into treatments – and just as critically, from bed to bench side to guide and stimulate basic discoveries and understand the origins of disease. The observant clinician is often the source of a new idea that is translated into a new treatment.

A major NIH priority for the upcoming years is to rethink the technical and human infrastructure requirements for a more effective clinical research enterprise. A planning effort is underway to identify the major roadblocks and potential solutions. We will focus on a broad-based re-engineering effort with partnerships involving our sister Agencies, academic centers, community based professionals, industry, and patient groups. The ultimate goal of this effort will be to develop a more systematic and standardized national clinical research infrastructure with interoperable information systems to maximize the effectiveness of our investments in clinical investigations.

A primary concern is the slow and uneven implementation of clinical research advances into medical care and the inadequate feedback loop available to investigators for clinical outcomes in "real world" settings. The time it takes research advances to permeate routine patient care settings is far too long and implementation is disproportionately longer still in many minority communities.

Year after year, the NIH brings solid scientific evidence to the practice of medicine and the improvement of health. Research either confirms or tempers claims of effectiveness as shown by the recent results from the hormone therapy trials of the Women's Health Initiative. Despite generous Congressional budget increases, without a real effort at optimizing the efficiency of our national system of clinical research, the NIH will be unable to engage in all of the clinical trials

on the many new drugs, drug combinations, and diagnostic and prognostic tests that are rapidly filling the pipeline.

NIH must leverage its clinical research investments in order to learn as much as possible from large, expensive trials. The goal this effort is to design and implement a national clinical research infrastructure, which would integrate advances in clinical research informatics into the medical care setting and provide the capacity to share data resources. Such an ambitious national effort would permit data collected from patients in the health care system to be readily used to advance clinical and population-based research.

The construction of such an infrastructure would be complemented by the establishment of nationwide integrated clinical research network(s) comprised of scientists, physicians, and patients in either specific disease categories or population categories. This could support the staging of longitudinal and epidemiologic studies. As envisioned, the national network would integrate communication and data sharing among clinical research centers, General Clinical Research Centers; academic health centers; the pharmaceutical, biotechnology, and managed care industries; foundations; and physicians on the front lines of care.

While shared data will jump start research innovation, this effort will move forward with special attention to the protection of human subjects and safeguarding the privacy individually identifiable health information. Issues about the credentialing of investigators and the establishment of standards for the conduct of clinical research will be part of reconfiguring the field.

Finally, the expansion and support of the clinical research workforce represents the most threatened component of the national clinical research effort. Cultural aspects of the clinical research enterprise must be reconfigured – away from the traditional emphasis on grants performed by individual scientists to an increasing reliance on the combination of clinical, behavioral, population, and basic biomedical sciences in a collaborative team that incorporates multiple cross-disciplinary skills.

Creative approaches are called for, which will draw upon the expert skills of engineers, mathematicians, physicists, and computer scientists. Sweeping changes in career development will focus not just on physician-scientists, but on each member of the multidisciplinary team; thus including fields such as engineering, physics, nursing, mathematics, statistics, computer science, behavior, pharmacology, and epidemiology.

These multidisciplinary clinical research teams hold the future of medicine in their hands. NIH is committed to meeting the challenge to inspire young investigators of many disciplines to join the clinical research teams needed to conquer illness and disease in our century.

Science Advances

The scientific advances highlighted here resulted from NIH-funded research in 2002. Most represent one of two categories: the development of new and improved treatments that will have an immediate impact on public health; or fundamental knowledge critical to the discovery process that holds the promise of leading to innovative life-saving treatments.

Another distinction to be found between the advances is that some have been widely disseminated and featured in the popular press because of the high-profile nature of, and public interest in the topic. Conversely, many studies receive much less attention even though the final results may have a major impact on the public health and health care of the American people.

An example of the latter type of advance was a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women that was stopped early due to an increased risk of invasive breast cancer from the treatment, known as hormone replacement therapy (HRT). The large multi-center trial, a component of the Women's Health Initiative (WHI), also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit. The study, which was scheduled to run until 2005, was stopped after an average follow-up of 5.2 years. Impressively, the WHI involves over 161,000 women who are participating in a set of clinical trials designed to test promising but unproven preventive measures for heart disease, breast and colorectal cancer, and osteoporosis.

Thus, the NIH-supported science advances below range from cutting edge technical innovations and unique discoveries generated in a single laboratory to large, long term multi-center clinical trials testing drugs and therapies affecting millions of Americans.

Imaging techniques improve Alzheimer's disease diagnosis and treatment. Early and precise diagnosis of Alzheimer's disease (AD) can benefit affected individuals and their families. Refinement of positron emission tomography (PET) and magnetic resonance imaging (MRI) is not only improving our ability to characterize and diagnose the disease early, but also giving us new options for tracking the effectiveness of treatments in the brain. Investigators in several recent studies identified specific metabolic changes in the brain that are characteristic of AD. In one study, they demonstrated that measuring patterns of brain changes can be used to diagnose AD with a high degree of accuracy. Additionally, researchers found that the atrophy of several areas of the brain measured by MRI correlate with a decline in brain activity and cognitive ability. Therefore, MRI may be useful for identifying early AD or for clinically assessing AD-related cognitive function. These and other techniques may facilitate early diagnosis of AD and provide effective methods for tracking the effectiveness of new treatment approaches.

Tracking down auditory hallucinations in schizophrenia. Hallucinations, which are among the most dramatic, disabling, and conspicuous symptoms of schizophrenia, are poorly understood. Because schizophrenic hallucinations are often auditory, researchers are focusing on the part of the brain that "hears" (auditory cortex). One theory about hallucinations is that they are the patient's own thoughts which are misperceived as real words spoken by someone else. In healthy individuals, the brain seems to be able to signal the auditory cortex that the speech it perceives is coming from the self, rather than from outside. If this signal fails to occur when the person is speaking or thinking, the person "hallucinates" that they are hearing a voice. NIH-funded investigators have localized the part of the brain possibly responsible for this activity. These findings might one day permit researchers to develop medical or surgical treatments to enhance the missing signal and eliminate the hallucinations, which have such devastating effects on schizophrenics and their families.

Trial demonstrates that type 2 diabetes can be prevented or delayed. Type 2 diabetes affects almost eight percent of U.S. adults. This percentage is likely to increase dramatically as the population ages and becomes more sedentary and overweight. If this trend continues, a frightening new wave of type 2 diabetes will threaten not only the health of Americans, but also the health care system itself. Researchers tested the effectiveness of drug and lifestyle interventions in preventing type 2 diabetes in an at-risk population. They compared three groups: those who received standard lifestyle recommendations plus metformin (a drug used to treat diabetes); those who received standard lifestyle recommendations plus a placebo (inactive) drug; and those who participated in an intensive program of lifestyle modification, including both diet and exercise interventions. The intensive lifestyle modification reduced the incidence of diabetes by 58 percent. Treatment with metformin reduced the incidence by 31 percent compared to the placebo group. The diet and exercise intervention was significantly more successful in preventing diabetes than metformin, especially among older participants. Researchers saw similar results in all the racial and ethnic groups who participated and in men and women. By using these new tools, physicians and other providers can help stem the rising tide of type 2 diabetes that is threatening the public health in the U.S.

Potential new treatment preserves insulin production in recent-onset type 1 diabetes.

In type 1 diabetes, the patient's immune system attacks and destroys the insulin-producing beta cells of the pancreas, leaving the patient unable to produce enough insulin to maintain normal blood sugar levels. A recent small-scale clinical trial offers hope for those newly-diagnosed with type 1 diabetes. Researchers injected 12 patients who were diagnosed within the previous six weeks with a modified form of an antibody which suppresses the immune system's destructive T cells and stimulates the production of protective immune-signaling molecules. Nine of the 12 antibody-treated patients maintained or improved production of their own insulin for one year following diagnosis. Preservation of beta cell function is important because patients with diabetes who can still produce insulin can better control blood sugar and have less risk of low blood sugar reactions than patients with little or no ability to produce insulin. Researchers will now test this encouraging preliminary finding in more patients. If the treatment proves effective in new-onset diabetes patients in larger trials, researchers will study disease-free individuals at

high risk for type 1 diabetes to determine whether this novel antibody treatment may actually prevent the disease from ever developing.

Battling anthrax toxins. Knowledge of the structure and action of the multiple anthrax toxins will allow researchers to develop new and better drugs. NIH-supported researchers recently made several major discoveries about the disease-causing proteins of anthrax. One set of studies revealed that a toxin called lethal factor (LF) lets anthrax evade the immune system of an infected individual by inhibiting cells (macrophages) that normally signal the immune system to attack the anthrax bacteria. This information may lead to discovery of a drug or agent to block the action of LF. A second set of studies revealed the structure of another anthrax toxin called edema factor, which causes potentially lethal swelling and makes LF more toxic. Determining the structure of edema factor revealed that the toxin changes its shape dramatically upon binding to a normal cellular protein (calmodulin) to show the toxic "pocket" of the anthrax protein. Because it contains a deep, narrow pocket, the activated edema factor appears an ideal drug target. Determining how LF acts as well as the physical structure of the edema factor are significant steps in developing drugs to combat anthrax infection.

Genetic differences found in African American and European American lupus families.

One of the many mysteries of health disparities is that no one knows why more African Americans die of systemic lupus erythematosus (or lupus) and develop more severe complications, such as kidney failure, compared with people of European descent. NIH-supported researchers are studying the inherited component of lupus to identify the specific genes that predispose African Americans to develop lupus. By studying different segments of DNA on the chromosomes of African American and European American families, researchers determined that African Americans have different genetic risks for developing lupus. Researchers found that a region of chromosome 1 is associated with the development of lupus in African American families. They also identified two regions of chromosome 11 associated with lupus in subsets of the African American families. In European American families, researchers found a DNA segment near the top of chromosome 4 that contributes to lupus. These results suggest that the genetic origins of lupus may differ in African Americans and European Americans and may explain why the disease sometimes has a more severe prognosis in African Americans.

Traditional diuretics better than newer medicines for treating hypertension. Results from the largest clinical trial ever conducted on reducing high blood pressure revealed that traditional diuretics work better than newer, more costlier medicines. About 24 million Americans take drugs to lower high blood pressure at an estimated annual cost of \$15.5 billion. Diuretic use would reduce that cost by approximately \$300 million per year. The finding also showed that the use of diuretics reduced the risk of complications from the newer drugs. Compared to participants taking the diuretic, those on the newer medication, known as an ACE inhibitor, had a 15 percent higher risk of stroke (40 percent for African Americans), 19 percent higher risk of developing heart failure, and a 10 percent higher risk of needing coronary artery bypass surgery. The study results provide important guidance to physicians on the best options for their patients. In addition, the study demonstrates the need for large clinical trials to reveal critical information

that significantly affects the health of many Americans afflicted with common conditions such as heart disease.

HIV selectively targets anti-HIV defense cells. Human immunodeficiency virus (HIV), the virus that causes Acquired Immunodeficiency Syndrome (AIDS), attacks the immune system and leaves the body vulnerable to a variety of life-threatening illnesses and cancers. Crucial immune cells are disabled and killed during the typical course of infection. These cells play a central role in the immune response of the body, signaling other cells in the immune system to perform their special functions. Building on knowledge that the immune system does not produce a strong response of these cells against HIV, researchers postulated, and the results of this study confirmed, that HIV infection preferentially infects the immune cells specifically designed to fight the virus at all stages of infection. This finding will help develop new and better ways to treat HIV-infected patients and aid in developing a more effective HIV vaccine.

High levels of homocysteine increase Alzheimer's disease risk but may be prevented by folic acid intake. Alzheimer's disease (AD) accounts for more than 70 percent of all cases of dementia. Thus, the identification of risk factors for the disease, especially those we can modify, is critically important. Interest is growing about factors in the blood that might underlie AD. Blood levels of homocysteine, a simple amino acid, emerged as a major blood vessel disease risk factor, suggesting that high levels of circulating homocysteine might be connected with AD. Folic acid deficiency results in increased levels of circulating homocysteine in the blood. Scientists are intrigued that increased folic acid intake might significantly reduce the vascular complications that contribute to AD. Participants in an NIH-supported study had homocysteine levels measured between 1979 and 1982. Eight years later, when the same individuals were examined for AD, researchers found that elevated homocysteine levels doubled the chance of AD. Further, they found that measuring homocysteine levels may predict AD before symptoms arise, offering opportunities to delay onset. In a related study, using a mouse model of AD, researchers found that animals fed a folic acid-deficient diet had elevated levels of homocysteine and a reduced number of neurons in a part of the brain critical for learning and memory. Since folic acid reduces homocysteine levels, increased folic acid intake may reduce AD risk. These basic and clinical research findings are opening doors of opportunity for new treatment approaches for a disease that has a devastating impact on families and individuals.

Vaccine developed against deadly hospital-acquired infection. *Staphylococcus aureus*, a bacterium, causes infection and death among hospital patients. *S. aureus* infection causes illnesses ranging from minor skin infection to life-threatening diseases such as severe pneumonia, meningitis, bone and joint infections, and infections of the heart and bloodstream. Many strains of *S. aureus* are resistant to methicillin and vancomycin, the antibiotics used to treat it. The recently designed vaccine circumvents bacterial defenses, which previously made vaccine development impossible. Tests in mice and humans both demonstrated that the new vaccine produces antibodies that inactivate the bacteria. Given the alarming resistance of *S. aureus* strains to the existing antibiotics, the vaccine may prevent the thousands of serious *S. aureus* infections that occur each year in hospitals across the United States.

Pathology of Tuberculosis revealed: a potential vaccine target. Tuberculosis (TB) infects about one-third of the world's population and kills more than two million people each year. In about 10 percent of those infected, the way the Mycobacterium (MTB) evolves from a latent infection to a deadly disease is unknown. NIH-supported scientists from India and the United States, using a newly developed MTB strain – with a mutated gene – recently shed light on the pathology of TB. In mice, the mutant strain infects, multiplies and survives in the lungs and spleen like the standard MTB, but does not stimulate inflammation, spark an immune response, or cause tissue damage as does the original strain. Analysis of the mutant gene indicates that it controls, directly or indirectly, the function of almost 200 genes. Many of these regulated genes appear to comprise a system that MTB uses to protect itself from heat, oxidation and other environmental stresses. This study suggests that strains containing genetic mutations that interfere with tissue damage could serve as vaccine candidates for TB. Moreover, the identified MTB environmental defense system may also serve as a model for new drug targets.

Effective intervention for long-term reduction in college drinking. College drinking is a major public health problem, which can result in violence, date rape, accidents, and even death. NIH-funded researchers found that high-risk students who received a brief counseling session drank less alcohol and experienced far fewer alcohol-related problems than did high-risk students who did not receive the intervention, even after four years. The most significant effect of the intervention was reducing the consequences of drinking, consistent with the overall goal of harm reduction. Alcohol consumption also declined in the control group, suggesting that much of the heavy drinking done by college students is transitory. This finding suggests that brief interventions can hasten the naturally occurring decline in consumption. Future studies will identify the critical content and delivery components of the brief intervention.

Brief inactivation of a cancer gene permanently reverses tumor cell production. Oncogenes are mutated normal genes responsible for the uncontrolled cell growth typical of cancer. Cancer therapies designed to turn off oncogenes might have serious toxicities because they also target normal cells. Recently, scientists demonstrated in animal studies that brief inactivation of the MYC oncogene during cancer treatment may lead to the sustained regression of tumors without inducing significant toxicity. These researchers devised a way to conditionally activate or deactivate the MYC oncogene in a mouse model. The studies demonstrated that in bone tumor-bearing mice, brief inactivation of MYC slowed tumor cell growth as well as the development of the bone cancer cells into mature bone. Surprisingly, subsequent re-activation of MYC not only failed to induce regrowth of the tumors, but also produced cell death. Researchers observed similar results in laboratory tests using human bone cancer cells. This study suggests that the intermittent and brief inactivation of oncogenes may lead the way to new more effective, nontoxic cancer therapeutics.

Adult neural stem cells make functional neurons. Regeneration of neurons, a challenging scientific problem, is a key treatment strategy for many neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and stroke, to mention a few. NIH-supported research demonstrated in animal studies that neural stem cells derived from adult brain can produce

functional neurons as well as integrate into the circuitry of at least some brain regions. In one study, scientists tracked adult neural stem cells after injection into one brain region of animal models. The results showed that two days after the injection, the labeled cells looked like immature neurons. However, by one month, they looked and behaved like authentic, mature neurons. Closer examination revealed that the new neurons had similar properties to their mature neighbors and that they received input from other cells. In a second study, researchers isolated stem cells from the adult rat brain and cultured them along with normal neurons. The stem cells formed neurons with axons and dendrites, which are structures critical for communicating with other cells. In fact, these stem cell-derived neurons made functional connections, called synapses, with normal neurons and with each other. They also released neurotransmitters, the chemical mediators of neuronal communication. The generation of new functional neurons from neural stem cells, either from those in the brain or from those transplanted into the brain, could some day be harnessed to regenerate damaged brain tissue, to replace dying neurons, or to enhance the brain's response to age-related impairments.

Direct brain control of neuroprosthetic devices. Decades ago, when scientists first recorded the activity of nerve cells in the brain that control movement, researchers speculated that they might harness these brain signals to directly control neuroprosthetic devices. Scientists recently devised a system that brings this goal much closer. They implanted electrodes in the brains of monkeys and developed a sophisticated computer program to interpret the recorded signals. With this system, monkeys, using thought alone, could quickly and accurately move a cursor on a computer screen. This system worked without any special training and allowed control in a virtual 3-dimensional world.

Minimizing brain damage after stroke. Direct intervention to minimize damage to the brain after a stroke is difficult due to the presence of the blood-brain barrier (BBB). It protects the brain from toxic substances, but also prevents most potentially therapeutic drugs from entering the brain. Tiny blood vessels that make up the BBB contain specific transport systems which latch onto the molecules that the brain needs from the general circulation and carry only those chemicals into the brain. NIH-supported scientists have developed a “Trojan horse” strategy to deliver drugs across the BBB. The idea is to trick specific transport systems into carrying a drug into the brain. In animal studies, when a “Trojan horse” version of basic fibroblast growth factor, a natural survival promoting molecule, was given to rats intravenously an hour after an induced stroke, the area of damaged brain was reduced by 70 percent. This study offers a promising approach for minimizing brain damage in stroke patients.

Story of Discovery

Developing a Vaccine for West Nile Virus

West Nile Virus (WNV) belongs to a group of disease-causing viruses known as flaviviruses, which are spread by insects, usually mosquitoes. Most human infections from the WNV are mild, causing fever, headache, and body aches, often accompanied by skin rash and swollen lymph nodes. However, the virus can cause life threatening encephalitis (inflammation of the brain) or meningitis (inflammation of the lining of the brain and spinal cord). Outside of mosquito control, there is neither a treatment for encephalitis nor a preventive vaccine for WNV infection available at the present time. Faced with the possibility of a serious WNV epidemic, NIH-funded researchers sprang into action and have successfully developed a vaccine to protect against WNV infection.

Basic research on newly emerging microbes has enabled rapid progress in the development of a WNV vaccine. WNV vaccine development has also benefited from the fact that WNV belongs to the group of flaviviruses, which have many characteristics in common.

These similarities have allowed scientists to build on earlier discoveries about other flaviviruses that are closely related to WNV, including Japanese encephalitis virus (JEV), St. Louis encephalitis virus (SLEV), yellow fever virus (YFV), and dengue virus. Specifically, the success of control of yellow fever and Japanese encephalitis with well-organized vaccination campaigns centered on an efficacious vaccine gave scientists a model on which to build.

An important first step was the observation that hamsters, and to a lesser degree mice, were good models for West Nile (WN) disease. NIH-funded investigators at the University of Texas Medical Branch, Galveston, sought to uncover the degree of protection that candidate WN, and other licensed flavivirus, vaccines might have against WNV. They found that prototype WN vaccines completely protected hamsters, and, surprisingly, vaccines for Japanese encephalitis and yellow fever vaccines afforded the hamsters partial protection. Thus, researchers discovered a new model for developing WN vaccines, one they could use to test the efficacy of a new candidate vaccine (or a new antiviral medicine).

NIH supports a number of vaccine approaches. One of the earliest, started in 1999, was a fast-track project to develop a WNV vaccine candidate with the company Acambis, Inc. Since then, scientists have developed a prototype vaccine that showed promise in animal studies. The prototype uses, as the backbone, a vaccine licensed for preventing yellow fever (caused by another flavivirus). For the WNV vaccine, researchers substituted the surface protein of WNV for the deleted yellow fever virus protein. This method of creating chimeric (two genetically distinct organisms) flavivirus vaccines is also used to develop a vaccine for dengue and JEV. Pre-clinical evaluations of the Acambis vaccine in hamsters, mice, monkeys, and horses showed encouraging results. The company is moving ahead with Phase I trials. Vaccine is now in production and an investigational new drug (IND) application will be filed with the Food and Drug Administration. Trials could begin in early 2003.

Other NIH scientists and collaborators from the Walter Reed Army Institute of Research (WRAIR) capitalized on recent advances in recombinant DNA technology and previous research on another flavivirus (dengue virus) to produce a new candidate WNV vaccine. This NIH team has already successfully replaced key genes of different flaviviruses with those of dengue virus type 4 (DEN4). Unlike many flaviviruses, DEN4 does not cause disease in the brain. The resulting weakened, or attenuated, virus strains were safer for use in a vaccine but still protective. The NIH-WRAIR research team then combined genes from WNV and DEN4. While this hybrid virus did not infect the brain, a single dose still stimulated a strong immune response. When tested in mice, the hybrid vaccine protected all animals against lethal WNV infection.

The next step for the NIH-WRAIR research team calls for testing the promising hybrid vaccine in monkeys. Vaccine trials in humans are expected to progress rapidly because a dengue virus used in the hybrid virus already has been proven safe in people. Studies by other NIH-supported scientists are also underway on a DNA vaccine, as well as a protein vaccine, approach.

**National Institutes of Health
RD&E Funding by Research Theme
Competing Requests for Grant Applications and
Requests for Proposals for R&D Contracts
FY 2004 President's Budget
(Dollars in Thousands)**

Research Theme	Competing RFAs and RFPs for R&D contracts
I. Working Toward Independence	\$11,100
II. Rallying the Armies of Compassion	4,500
III. No Child Left Behind	2,500
IV. Promoting Active Aging and Improving Long-Term Care	26,100
V. Protecting and Empowering Specific Populations	2,838
VI. Helping the Uninsured and Increasing Access to Health Insurance	0
VII. Realizing the Possibilities of 21st Century Health Care	61,200
VIII. Ensuring our Homeland is Prepared to Respond to Health Emergencies	553,000
IX. Understanding Health Differences and Disparities--Closing the Gaps	45,800
X. Preventing Disease, Illness, and Injury	233,020
XI. Agency-Specific Priorities (all other progs. 1/)	26,722,707
Buildings and Facilities	80,000
Total Budget Request	27,742,765

1/ Other Programs - Includes grants, intramural, other R&D contracts, RMS

Support for categories I-X is also accomplished through investigator-initiated research, the most prevalent mechanism NIH uses to support research. Through agreement with the Office of the Assistant Secretary for Planning and Evaluation, these investigator-initiated activities are not included in categories I-X.

Research Coordination Council

Through its participation in the Department's Research Coordination Council (RCC), the NIH has been able to identify opportunities for enhanced coordination that will contribute to a number of the President's and the Secretary's research goals. For example, plans are underway to expand the use of the NIH Early Notification System (ENS) to facilitate information sharing across the Department for Requests for Applications, Program Announcements, and Early Concept Announcements. This system, effectively used for many years by NIH and other registered users, serves as an electronic gateway to help improve cooperation and collaboration on research initiatives that span the research programs and interests of multiple NIH Institutes and Centers. To improve coordination of the Department's research activities, each Operating Division (OPDIV) will identify a contact person for the ENS who will determine if their proposed solicitations should be entered into the ENS and coordinate review within their OPDIV. To assist in this effort, the NIH will offer training sessions of the ENS to the various agency contacts.

NIH's participation in the RCC also will foster increased collaboration and coordination with the Indian Health Service (IHS) in the area of health disparities. The IHS is responsible for identifying best practices for encouraging preventive behaviors and providing health services to the American Indian/Alaska Native population. The IHS has expressed interest in ensuring that needs of their service populations are sufficiently addressed in research funded by other HHS agencies. NIH and other OPDIVs will continue and expand, as appropriate, research collaborations with IHS and tribal organizations and will notify IHS of relevant research projects.

In fiscal year 2004, the Department anticipates expanding its commitment to supporting the most effective and appropriate translation, dissemination, and implementation of research products and science-based health information to health care providers, consumers, educators, and policy makers who can benefit from such findings. NIH and other OPDIVs will work with the RCC to identify the most effective ways to communicate this information that will increase the likelihood of its adoption in practice. We will continue to evaluate community-based participatory research models to better translate research findings into appropriate tools to improve health and to test the effectiveness of health interventions in diverse communities where local health care capacity and resources may be limited. The RCC will continue to provide a forum for developing new ideas to enable HHS components, including the NIH, to take advantage of every opportunity for efficiency in the support and conduct of the Department's research programs.

Over the past five years, the Congress, the Administration, and the American people have demonstrated their strong commitment to public sector research by their efforts to double the NIH budget. As a result, the NIH now funds nearly 10,000 more research grants than it did before doubling began – 10,000 more ideas that could lead to vaccines, cures, and treatments to improve human health. The NIH now funds 40 percent more research centers than it did in 1998. Such centers can provide the catalyst for researchers of many backgrounds to come together to solve fundamental science problems or develop novel cures. The NIH can now support the training of 1,500 more scientists each year than it could in 1998. This investment will help ensure there are enough trained professionals ready to turn today's research advances into tomorrow's treatments, diagnostics, vaccines, and cures. Although the path from scientific concept to bedside is often not linear or predictable, we can say with confidence that today's research promises to yield a deeper understanding of human biology, which will help usher in a new era of medicine.

FY 2004 BUDGET POLICY

The FY 2004 program level for the NIH, based on current law, is \$27,893 million, an increase of \$549 million or 2 percent over the FY 2003 Amended President's Budget. Included in this request is \$79 million to be requested from the Veteran's Administration/Housing and Urban Development Appropriations Subcommittee for the Superfund research program and \$150 million for the Type I Diabetes Initiative appropriated through P.L. 107-360. When adjusted for one-time facilities costs in FY 2003, the total available for NIH non-biodefense research programs increases by 4.3 percent. The NIH President's Budget authority request to the Labor/Health and Human Services/Education Appropriations Subcommittee is \$27,664 million.

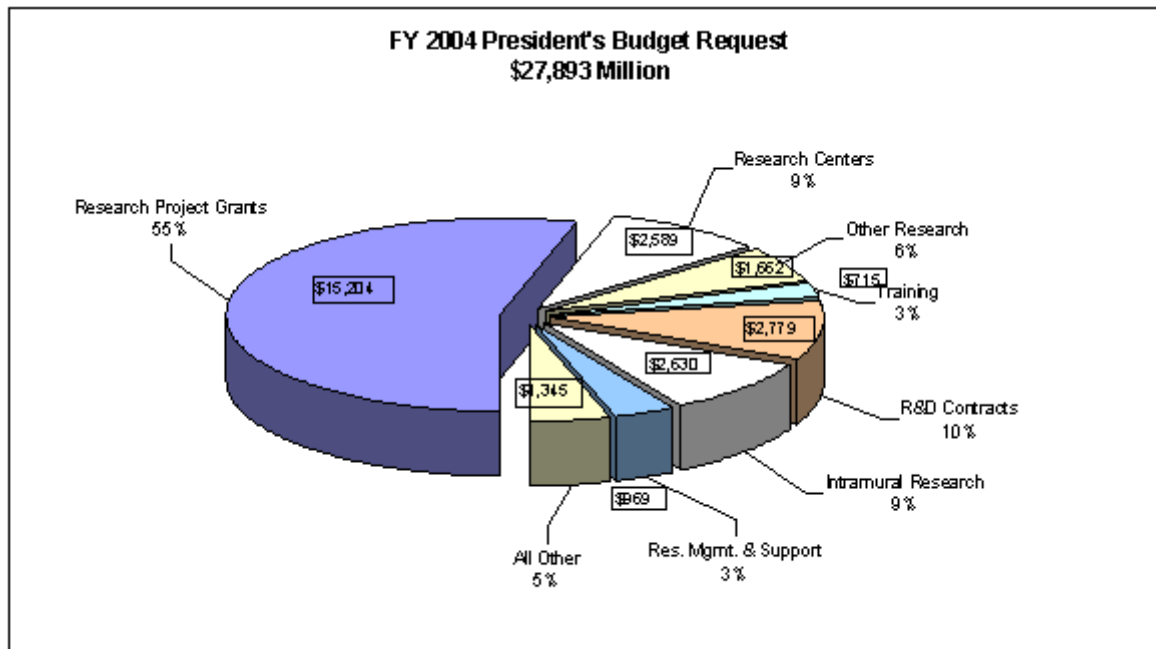
The recent, deliberate exposure of the civilian population to anthrax spores revealed weaknesses in our nation's defenses against bioterrorism. Biomedical research is an important component of the overall effort to protect the United States against bioterrorism, by improving our ability to rapidly diagnose outbreaks, provide vaccines and immunotherapies to prevent adverse health consequences of attacks, and provide drugs and biologics to cure disease caused by agents of bioterrorism.

The FY 2004 President's Budget request continues our efforts to expand our nation's biodefense capacity by providing \$1,625 million for biodefense research. The apparent decrease from the FY 2003 Amended President's Budget is the result of the accelerated funding of new biodefense facilities in FY 2003. Excluding these facilities funds and the one-time anthrax vaccine procurement from FY 2003, support for biodefense research increases by 117 percent. Under the leadership of the National Institute of Allergy and Infectious Diseases, NIH has developed a strategic plan to effectively target this proposed increase in several critical areas:

- Expanding basic research, including the addition of four Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases to provide and maintain the research and development capacity necessary for identifying and responding to emerging diseases and bioterrorism events;
- Expanding the number of candidate drugs and vaccines under research using the FDA's "animal model rule"; this rule is the principal approach to showing scientific "proof of concept" for a candidate drug or vaccine that is under development as a countermeasure to a potential agent of bioterrorism. NIH will also increase its interactions with collaborative partners in industry to foster translational research; and
- Expanding clinical research projects to support Phase I and II clinical trials of candidate vaccines/drugs, including a next generation smallpox vaccine, a plague vaccine and an ebola vaccine.

Support for AIDS research will increase by \$110 million, or 4 percent over the FY 2003 Amended President's Budget, for a total of \$2,870 million.

The budget request for NIH also includes \$100 million in NIAID to continue HHS contributions initiated in FY 2002 to the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis.



Mechanism Discussion

The funding of basic biomedical research through supporting investigator-initiated research, including Research Project Grants (RPGs) and ensuring an adequate number of new researchers with new ideas, remain NIH's highest priorities. The FY 2004 NIH Request would support 10,509 competing RPGs, an increase of 344 grants over the FY 2003 Amended President's Budget, for \$3,819 million. NIH will maintain our investment in medical research by providing an aggregate average cost increase of 2.7 percent for RPGs. A total of 322 competing RPGs, mostly small grants, will receive full funding in FY 2004. The Small Business Technology Transfer Research program (STTR) reflects P.L. 107-50, to increase the STTR set aside from 0.15 percent of the R&D base to 0.30 percent, beginning in FY 2004.

Research Centers increase by \$167 million and 6.9 percent in the FY 2004 President's Budget request. In FY 2004, NIAID anticipates establishing an additional four Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases to provide and maintain the research and development capacity necessary for identifying and responding to emerging diseases and bioterrorism events. These additional centers are estimated to cost \$70 million in FY 2004. Also included in this mechanism is an increase of \$25 million, for a total of \$210 million in support for the Institutional Development Award (IDeA) program. This increase supports NIH's

continuing efforts to develop a critical mass of competitive biomedical researchers in states that have not fully participated in NIH research funding in the past.

The NIH will support an additional 80 Full-Time Training Positions (FTTPs) in the Ruth L. Kirschstein National Research Service Award program in FY 2004, for a total of 17,197 FTTPs, while overall funding increases by \$22 million. The increase of 80 FTTPs will support additional trainees for biodefense research (+74 FTTPs) and additional trainees in child health (+5 FTTPs) and bioinformatics and bioengineering research (+1 FTTP).

The FY 2004 President's Budget increases NRSA stipends by proposing stipend increases of 4 percent for pre-doctoral trainees and a decreasing scale of 4 through 1 percent for post-doctoral recipients, depending on years of experience. This would raise stipends for predoctoral trainees from the FY 2003 level of \$18,876 to \$19,632 in FY 2004. Stipends for postdoctoral fellows which ranged from \$32,340 to \$49,224 in FY 2003 depending on years of experience would increase to a range of \$33,624 to \$49,584.

Research and Development (R&D) contracts increase by \$348 million and 14.3 percent compared to the FY 2003 Amended President's Budget request. Non-biodefense R&D contracts increase by \$147 million and 7.7%. The request for NIH includes an additional \$25 million for a total of up to \$50 million in FY 2004 for implementation of the provisions of the Best Pharmaceuticals for Children Act. NIH will contract for studies cited by FDA as needed to provide dosage, safety, and effectiveness data in children to permit labeling of off-patent drugs for pediatric use when manufacturers decline to perform the studies. The NIH and FDA are working cooperatively, with expert outside advice, to identify and prioritize drugs in this category that most need pediatric studies; identify the specific studies that need to be done; issue requests to manufacturers to perform the studies; and, if they decline to do the testing, issue requests for proposals (RFPs) from NIH to perform these studies under contract. Some drugs have already reached the stage where RFPs are being prepared that will be issued in FY 2003, and many others are close behind in the process. The funds requested in FY 2004 will allow this testing to proceed.

The Intramural Research program will increase by \$81 million, or 3.2 percent. Within this increase, \$31 million will support increased Biodefense research activities in the National Institute of Allergy and Infectious Diseases (NIAID). Non-biodefense Intramural Research increases by \$50 million.

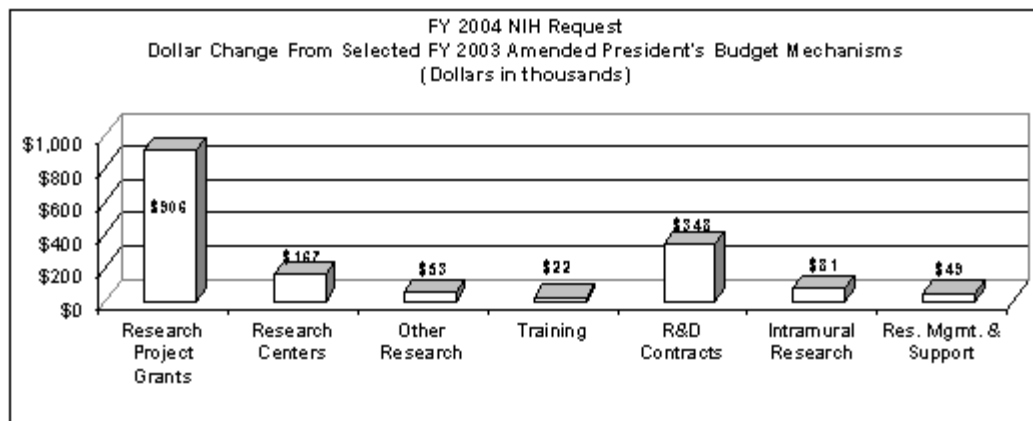
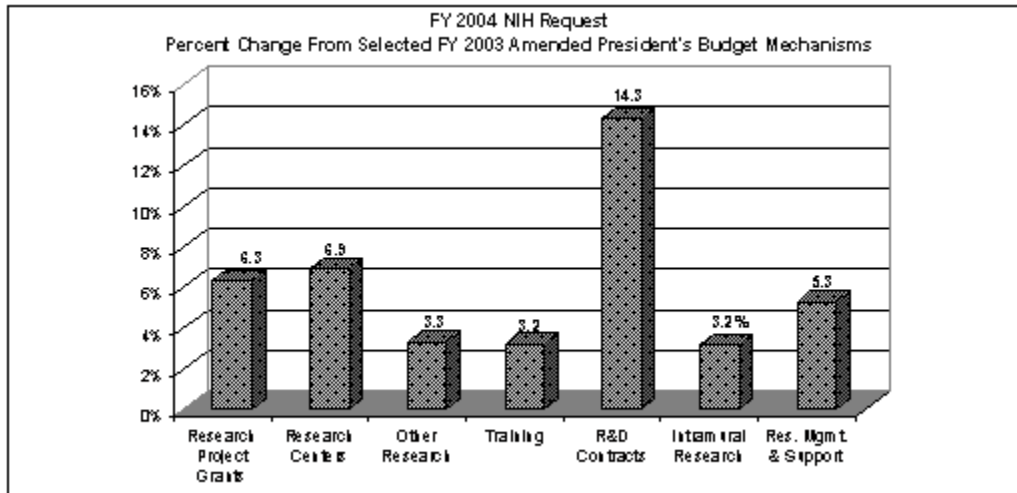
Research Management and Support (RMS) will increase by \$49 million, or 5.3 percent. This will provide NIH with sufficient capacity to manage its research portfolios, and to ensure appropriate stewardship of all funds. Within this increase, \$33 million will provide for increased scientific management and program oversight for biodefense activities in the NIAID. Non-biodefense RMS increases by \$16 million.

The doubling of the NIH budget over the past five years has allowed NIH to undertake an aggressive building campaign to provide researchers with the laboratories of the 21st century. With funding for the last major programs, the Mark O. Hatfield Clinical Research Center and the John Edward Porter National Neurosciences Research Center, completed in the FY 2003 Amended President's Budget request, the FY 2004 President's Budget provides \$80 million for ongoing repairs and improvements to existing NIH facilities.

There are two types of costs for major facilities; costs that must be funded through buildings and facilities appropriations, and limited improvements/alterations that can be funded through operating budgets. For costs funded through operating budgets, NIH follows the funding policies and guidelines contained in the *PHS Facilities Manual*, Chapter 2-1 (Funding Sources and Definitions). The *PHS Facilities Manual* authorizes the use of agency annual operating appropriations for limited improvements and alterations directly related to the installation of special purpose equipment. These improvements may include converting existing spaces such as laboratories to a different special purpose or function. This includes structural alterations (replacement or rearrangement of walls and partitions) and installation, operation and use of special-purpose equipment that is defined in Chapter 2-1 as casework, sinks, fumehoods, etc. This chapter also authorizes the use of operating funds for minor office alterations. NIH justifications have not separately identified these costs, nor explicitly associated them with specific major facility projects.

HHS will update and reissue its policy for use of operating funds on facilities projects to eliminate misinterpretation regarding the scope and limitation on the use of agency operating funds for renovations and collateral costs associated with major construction projects. This could lead to revision in the way all operating divisions present major facility costs in budgets, to assure that both the Executive Branch and the Legislative Branch have the information needed to make informed decisions. The purpose is to assure that agencies fully articulate the total costs of each proposed new construction project, including both the use of NIH Buildings and Facilities funds and IC operating funds. Another goal is to be able to appropriately budget for facilities costs that are integral to NIH fulfilling its mission.

The Office of the Director increases by \$44 million, of which \$35 million has been reserved in the NIH Director's Discretionary Fund for future allocation later in the budget process. The NIH Director is convening a series of small meetings with scientists from various disciplines and areas of investigation, with the goal of identifying some of the major and cross-cutting challenges in biomedical research today that can be specifically addressed by NIH. These meetings, which are composed of Institute Directors, extramural and intramural scientists, and NIH program staff, will explore the major knowledge gaps and systemic roadblocks in the current and future study of human biology and disease. As the working groups identify these roadblocks and develop strategies to address them, NIH plans to allocate these funds to the Institutes and Centers in FY 2004.



Other Key Issues

The epidemic of obesity threatens the Nation's health by sharply increasing the incidence of type 2 diabetes, fatty liver disease, kidney failure, cardiovascular and other diseases. However, dramatic advances in our understanding of regulation of appetite and weight offer new opportunities to develop methods to treat obesity and to prevent type 2 diabetes and other obesity-related diseases. The FY 2004 President's budget request includes an increase of \$14 million for expanded trans-NIH research programs in obesity and diabetes

As part of our ongoing review of NIH business processes, NIH management conducted an in-depth review of the funding process for the NIH centralized administrative activities. As a result of this review, we are consolidating certain administrative policy functions in the Office of the Director, and have made a budget neutral adjustment. Current year and prior year figures for each relevant appropriation account have been comparably adjusted in FY 2002 and FY 2003.

The NIH FY 2004 President's Budget request includes funding to support Departmental efforts to improve the HHS Information Technology Enterprise Infrastructure. The request includes funds to support an enterprise approach to investing in key information technology infrastructure such as security and network modernization. These investments will enable HHS programs to carry-out their missions more securely and at a lower cost. Agency funds will be combined with resources in the Information Technology Security and Innovation Fund to promote collaboration in planning and project management and to achieve common goals such as secure and reliable communication and lower costs for the purchase and maintenance of hardware and software.

Included within the overall budget amount is continued funding for four NIH-wide "Enterprise" Information Technology projects: Electronic Research Administration (eRA) for grants processing; the NIH Business System for a wide-range of financial and other administrative functions; the NIH portion of the HHS Enterprise Human Resources and Payroll system (EHRP); and, the Clinical Research Information System (CRIS).

Also included is \$7.7 million to support the United Financial Management System (UFMS), which will be implemented to replace five legacy accounting systems currently used across the Operating Divisions. The UFMS will integrate the Department's financial management structure and provide HHS leaders with a more timely and coordinated view of critical financial management information. It will also promote the consolidation of accounting operations and thereby reduce substantially the cost of providing accounting services throughout HHS. Similarly, UFMS, by generating timely, reliable and consistent financial information, will enable OPDIV Heads and program administrators to make more timely and informed decisions regarding their operations.

The FY 2004 President's Budget request reflects a \$109 million reduction in the Information Technology (IT) Budget, which incorporates savings from ongoing IT consolidation efforts, including the streamlining or elimination of IT projects. NIH will fully implement Information Technology (IT) infrastructure consolidation by October 2003, therefore reducing infrastructure expenditure in FY 2004.

In FY 2004, NIH is requesting an additional 125 FTEs to support biodefense research activities and provide for management and oversight of the biodefense research program. NIH's FY 2004 budget supports the President's Management Agenda and includes \$41 million in cost savings from consolidating administrative functions, organizational layering to speed decision making processes, competitive sourcing, implementation of effective workforce planning and human

capital management strategies, and adoption of other economies and efficiencies in administrative operations.

FULL-TIME EQUIVALENTS (FTEs)

	FY 2002 Actual	FY 2003 Amended P.B.	FY 2004 Request	Change FY 03 P.B./Request
Ceiling	17,140	17,683	17,516	-167
Ceiling Exempt	10	10	10	0
Total NIH	17,250	17,693	17,526	-167